REMARKS

Status of the Application

Claims 23-45 were pending in the application at the time the Office Action was mailed. Claims 34-38 and 45 were withdrawn. Claims 23-33 and 39-44 were rejected. No claims were allowed. Claims 23, 27-30, and 44 have been amended herein solely to expedite prosecution, and claims 24-26, 31-33, and 39-43 have been canceled. No new claims have been added. Therefore, claims 23, 27-30 and 44 are presently before the Examiner for consideration.

Specification/Sequence Compliance

The disclosure remains objected to for failure to comply with 37 CFR 1.821 through 1.825. Electronically filed herewith is a substitute Sequence Listing in computer readable form that complies with 37 CFR 1.822 and/or 1.823 and a Statement to Support Filing and Submission in Accordance with 37 C.F.R. §§ 1.821-1.825. The content of the substitute Sequence Listing electronically filed herewith is identical with the Sequence Listing filed on May 18, 2010. The substitute Sequence Listing filed herewith includes no new matter. Entry of this substitute Sequence Listing into the application is respectfully requested.

Accordingly, withdrawal of this objection is respectfully requested.

Claim Objections

According to the Office Action, should claim 39 be found allowable, claim 42 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. Claims 39 and 42 have been canceled herein.

Withdrawal of this objection is thus respectfully requested.

Nonstatutory Double Patenting

Claims 23-33 and 39-44 were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 7,667,027 to Schlingensiepen *et al.* ("Schlingensiepen I"), in view of U.S. Patent No. 6,153,388 to Reintgen *et al.* ("Reintgen"), U.S. Patent No. 5,550,316 to Mintz ("Mintz"), U.S. Patent No. 4,999,339 to Paradise *et al.* ("Paradise"), U.S. Patent No. 5,843,974 to Swift ("Swift"), U.S. Patent

No.6,787,161 to Aylward ("Aylward"), U.S. Patent No. 5,610,280 to Brandt *et al.* ("Brandt"), and U.S. Patent No. 5,369,527 to McCracken ("McCracken").

Applicants submit that the claims as amended herein are not obvious in view of the combination of eight patents. Claims 24-26, 31-33 and 39-43 have been canceled. Claim 23 (from which claims 27-29 depend) has been amended herein to recite "a method for inhibiting the formation of metastases in cancer treatment in a subject comprising the step of administering at least one TGF-beta2 antisense oligonucleotide selected from the group consisting of: SEQ ID NOs: 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47 and 48 to a subject, wherein said at least one oligonucleotide inhibits the formation of metastases in said subject." Claim 30 has been amended herein to recite a "method for cancer treatment comprising the step of administering at least one TGF-beta2 antisense oligonucleotide selected from the group consisting of SEQ ID NOs: 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47 and 48 to a subject, wherein said at least one TGF-beta2 antisense oligonucleotide inhibits the formation of metastases in said subject and said cancer is selected from the group consisting of: prostate cancer, colon cancer, and pancreatic cancer." Claim 44 has been amended herein to recite a "method for cancer metastasis treatment comprising the step of administering at least one TGF-beta2 antisense oligonucleotide selected from the group consisting of: SEQ ID NOs: 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47 and 48 to a subject, wherein said cancer is selected from the group consisting of colon cancer, prostate cancer, and pancreatic cancer."

The subject matter of currently amended claim 23 is directed to a *specific* selection of TGF-beta2 antisense oligonucleotides (i.e., SEQ ID NOs: 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47 and 48), which are able to inhibit the formation of metastasis and to treat metastasis. Even if the cited documents disclose TGF-beta2 antisense oligonucleotides, and/or the treatment of cancer by inhibiting TGF-beta, or the fact that cancer might include the formation of metastasis, none of these documents disclose or suggest the presently claimed *specific* selection of TGF-beta2 antisense oligonucleotides, which are able to inhibit the formation of metastasis and/or to treat metastasis. As not all TGF-beta2 antisense oligonucleotides are able to inhibit the formation of metastasis, the presently claimed method of inhibiting the formation of metastases in cancer treatment in a subject involving the use of

particular TGF-beta2 antisense oligonucleotides is not obvious in view of the combination of eight references. These references are discussed in greater detail below.

Regarding Schlingensiepen I, the Office Action asserts that this patent claims an antisense oligonucleotide having the sequence of SEQ ID NO:83 that hybridizes with the gene encoding TGF-β, and that SEQ ID NO:36 of the present application is identical to SEQ ID NO:83. As amended herein, the pending claims no longer recite SEQ ID NO:36.

Reintgen refers to a method for determining the presence of melanocytes in lymph node tissue. Reintgen does not refer to TGF-beta, to antisense oligonucleotides, or to the inhibition of metastases formation. Reintgen's disclosure that malignant melanoma is a form of skin cancer when combined with the remaining seven references fails to render the presently claimed invention obvious.

Mintz refers to a transgenic animal model for human cutaneous melanoma showing that factors present during wound healing may facilitate the formation of cutaneous melanoma. Mintz does not mention or provide any hint of TGF-beta2 or antisense technology at all, but describes Tyr-SV40E inducing melanoma. Hence, if a skilled person has the intention to find a solution to the problem underlying the present invention, i.e., finding a successful method for inhibiting the formation of metastases, the skilled person would not have any motivation to combine Schlingensiepen I and Mintz. The skilled person would not have expected that a TGF-beta 2 antisense oligonucleotide, in particular, any of SEQ ID No. 22 to 29, 31 to 35 or 37 to 48, would have an effect on the induction of Tyr-SV40 induced melanoma or metastatic melanoma formation.

Paradise relates to a method for therapeutic treatment of metastatic malignant melanoma comprising administering to a patient a synergistically effective amount of IL-2 and DTIC (dimethyl-triazeno-imidazolecarboxmid). Paradise, like Mintz, does not mention TGF-beta or antisense technology, and thus provides no hint to an effect of TGF-beta2 on the treatment of metastatic malignant melanoma, and therefore, the skilled person likewise would not have had any motivation to combine Schlingensiepen I and Paradise. The use of a TGF-beta2 antisense oligonucleotide for treating metastatic malignant melanoma is a very different concept from a combination therapy requiring IL-2 and DTIC, wherein the treatment is based on a synergistic effect of these two compounds.

Swift refers to a method of inhibiting melanoma, including metastatic melanoma, by administering benzothiophenes (2-phenyl-3-aroylbenzothiophenes). Swift does not mention TGF-beta or antisense technology, and thus provides no information or guidance about the use of TGF-beta2 antisense oligonucleotides in inhibiting the formation of metastases, and thus, also does not teach any selection of TGF-beta2 antisense oligonucleotides. Thus, a person skilled in the art would not be motivated to combine Schlingensiepen I and Swift. In the event a person skilled in the art would for some reason combine Schlingensiepen I and Swift, he or she would be taught to combine the TGF-beta antisense oligonucleotides of Schlingensiepen I with the benzothiophenes of Swift, resulting in a combination therapy, *not* in the selection of *specific* TGF-beta2 antisense oligonucleotides.

Aylward refers to a compound present in plants of the genus Euphorbia, which can be used in a method of treating cancer such as malignant melanoma etc. However, Aylward fails to even mention TGF-beta or antisense technology. Thus, Aylward is not at all directed to the use of TGF-beta2 antisense oligonucleotides for treating cancer, and does not give any hint to the inhibition of metastases formation. Therefore, as already mentioned for Swift, a person skilled in the art would hardly combine Schlingensiepen I and Aylward to find a solution to the problem underlying the present invention. If the skilled person would combine these documents, he or she would be guided again, at the most, in the direction of a combination therapy requiring a TGF-beta antisense oligonucleotide and a compound present in plants of the genus Euphorbia. The combination of these documents would not motivate the skilled person to find a *specific* selection of TGF-beta2 antisense oligonucleotides, able to inhibit the formation of metastases.

Brandt et al. relate to human monoclonal antibodies produced by the hybridoma cell line ECACC 900900703, and antibody derivatives thereof, which are all specifically binding to gangliosides GM3 and GD3, and only in a very low amount to GM1, GM2, GD1a, GD1b and GD2. These antibodies are for treating melanoma and bind to a certain extent to melanoma metastases. Brandt emphasizes that antibodies do not necessarily recognize all primary melanomas and melanoma metastases (see col. 1, l. 48-50) as discussed above for antisense nucleotides. Brandt fails to even mention TGF-beta or antisense technology. Brandt is thus completely silent on TGF-beta antisense oligonucleotides and their use in inhibiting the formation of metastases. Therefore, the skilled person would be motivated again to go the

direction of a combination therapy, in this case, a combination of a TGF-beta2 antisense oligonucleotide and an anti-GM3 or –GD3 antibody.

McCracken is directed to a melanoma detection apparatus, but does not provide information about a method of treatment of melanoma or of melanoma metastases. McCracken fails to even mention TGF-beta or antisense technology. Consequently, McCracken does not hint to the use of TGF-beta antisense oligonucleotides in such treatment and thus, a person skilled in the art would not be motivated to combine Schlingensiepen I and McCracken.

In summary, the combination of eight references does not disclose or even implicitly suggest the presently claimed *specific* selection of TGF-beta2 antisense oligonucleotides, which are able to inhibit the formation of metastasis and/or to treat metastasis. Applicants again assert that not all TGF-beta2 antisense oligonucleotides are able to inhibit the formation of metastasis, and that the presently claimed method of inhibiting the formation of metastases in cancer treatment in a subject involving the use of particular TGF-beta2 antisense oligonucleotides is not obvious in view of the combination of eight references.

Accordingly, withdrawal of the double patenting rejection is respectfully requested.

Claim Rejection Under 35 U.S.C. §112, second paragraph

Claim 40 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because of the recitation "and active derivatives thereof."

Claim 40 has been canceled herein. Accordingly, withdrawal of this rejection is respectfully requested.

Claim Rejection Under 35 U.S.C. §112, first paragraph

Claims 23, 24, 28-31, 39, 40 and 42-44 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. According to the Office Action, "[i]n certain embodiments, the cancer and thereby the particular subject in which the formation of metastases is inhibited may be any the many different cancers recited in claims 28-30, 39, 42 and 44, including melanoma" and "[i]n certain embodiments, the claims embrace and require the administration of any "TGF-beta 2 antagonist" to treat cancer." Claims 24, 31, 39, 40, 42 and 43 have been canceled herein. Claim 23 (from which claims 27- 29 depend) has

been amended herein to recite "a method for inhibiting the formation of metastases in cancer treatment in a subject comprising the step of administering at least one TGF-beta2 antisense oligonucleotide selected from the group consisting of: SEQ ID NOs: 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47 and 48 to a subject, wherein said at least one oligonucleotide inhibits the formation of metastases in said subject." Claim 30 has been amended herein to recite a "method for cancer treatment comprising the step of administering at least one TGF-beta2 antisense oligonucleotide selected from the group consisting of SEQ ID NOs: 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47 and 48 to a subject, wherein said at least one TGF-beta2 antisense oligonucleotide inhibits the formation of metastases in said subject and said cancer is selected from the group consisting of: prostate cancer, colon cancer, and pancreatic cancer." Similarly, claim 44 has been amended herein to recite a "method for cancer metastasis treatment comprising the step of administering at least one TGF-beta2 antisense oligonucleotide selected from the group consisting of: SEQ ID NOs: 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47 and 48 to a subject, wherein said cancer is selected from the group consisting of colon cancer, prostate cancer, and pancreatic cancer."

The subject matter of the claims as amended herein has been limited to the use of at least one TGF-beta2 antisense oligonucleotide of the group of: SEQ ID Nos. 22 to 29, 31-35 and 37 to 48. As the Examiner acknowledged in the previous office action that these oligonucleotides meet the written description requirement (see p. 15, 3rd paragraph of the previous office action), the claims as amended herein meet this requirement.

Accordingly, withdrawal of this rejection is respectfully requested.

Claim Rejections under 35 U.S.C. § 102

Claims 23-29 and 43 were rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 6,455,689 to Schlingensiepen *et al.* ("Schlingensiepen II"). Claims 23-25 and 43 were rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent Applic. Publ. No. 2004/0006030 to Monia *et al.* ("Monia"). Claims 24-26 and 43 have been canceled. Claim 23 (from which claims 27-29 depend), has been amended herein to recite "a method for cancer metastasis treatment comprising the step of administering at least one TGF-beta2 antisense oligonucleotide selected from the group consisting of: SEQ ID NOs: 22, 23, 24, 25, 26, 27, 28,

29, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47 and 48 to a subject, wherein said cancer is selected from the group consisting of colon cancer, prostate cancer, and pancreatic cancer." According to the Office Action, Schlingensiepen II anticipates the subject matter of the present invention as some of the oligonucleotides described in Schlingensiepen II are identical to the oligonucleotides disclosed in the present application. Thus, according to the Office Action, the oligonucleotides of Schlingensiepen II inherently disclose the properties of the oligonucleotides of the present invention. With regard to Monia, the Office Action states "[a]ll effects inherent to the use of antisense oligonucleotides that inhibit TGF-β2, including those recited in the instant claims, such as inhibition of metastasis formation, would necessarily be obtained by the administration of such oligonucleotides, since a compound and its properties are inseparable, and since, as evidenced by instant claim 25, the inhibition of TGF-β2 inhibits formation of metastases (MPEP 2112)."

Applicants respectfully disagree that Schlingensiepen II discloses the method of the present invention. The presently claimed TGF-beta2 antisense oligonucleotides of SEQ ID No. 22 to 29, 31-35 and 37 to 48 represent a *specific* selection of antisense oligonucleotides, none of which are disclosed in Schlingensiepen II. Similarly, Applicants respectfully disagree that Monia discloses the presently claimed invention. Monia discloses TGF beta2 antisense oligonucleotides to treat hyperproliferative diseases, but does not at all describe the specific oligonucleotides of the present invention, which inhibit the formation of metastases.

Because the cited references fail to disclose all claim limitations, withdrawal of these rejections is respectfully requested.

Claim Rejections Under 35 U.S.C. §103

Claims 28-33, 39-42 and 44 were rejected under 35 U.S.C. 103(a) as being unpatentable over Schlingensiepen II, and further in view of Reintgen, Mintz, Paradise, Swift, Aylward, Brandt, McCracken, U.S. Patent No. 6,120,763 to Fakhrai *et al.* ("Fakhrai I"); Monia; and Am J. Pathol. 145(1):97-104 by Reed *et al.* ("Reed"). According to the Office Action:

> Accordingly, it would have been prima facie obvious at the time of invention to administer any of the anti-TGF-β oligonucleotides disclosed by Schlingensiepen et al. to a subject having melanoma with the reasonable expectation any of the oligonucleotides could effectively treat a melanoma (i.e., skin carcinogenesis) in which TGF-β was involved, as

> taught by Schlingensiepen et al. In treating melanoma with any of the Schlinsiepen et al. antisense oligonucleotide compounds the practitioner would necessarily obtain all biological effects inherent to the compound, including those recited by the claims, such as inhibition of metastasis. A compound and its properties are inseparable. As evidenced claims 26, 27, 33 and 41 of the instant application, the antisense oligonucleotide of SEQ ID NO:30, and therefore of SEQ ID NO:72, is an oligonucleotide that inhibits the formation of metastases and production of TGF-beta2. As evidenced by claims 28 and 29, which recite the method of claim 23 for treating esophageal and neurofibroma cancer, the administration of an oligonucleotide within the scope of claim 23, such as that comprising SEQ ID NO:72 (SEQ ID NO:30), will treat esophageal and neurofibroma cancers and inhibit the formation of metastases in such cancers. As evidenced by page 1, line 13, of the specification, TGF-β is in fact a protein whose synthesis is involved in metastasis.

Claims 31-33 and 39-43 have been canceled. Claim 23 (from which claims 27- 29 depend) has been amended herein to recite "a method for cancer metastasis treatment comprising the step of administering at least one TGF-beta2 antisense oligonucleotide selected from the group consisting of: SEQ ID NOs: 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47 and 48 to a subject, wherein said cancer is selected from the group consisting of colon cancer, prostate cancer, and pancreatic cancer." Claim 30 has been amended herein to recite a "method for cancer treatment comprising the step of administering at least one TGF-beta2 antisense oligonucleotide selected from the group consisting of SEQ ID NOs: 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47 and 48 to a subject, wherein said at least one TGF-beta2 antisense oligonucleotide inhibits the formation of metastases in said subject and said cancer is selected from the group consisting of: prostate cancer, colon cancer, and pancreatic cancer." Claim 44 has been amended herein to recite a "method for cancer metastasis treatment comprising the step of administering at least one TGF-beta2 antisense oligonucleotide selected from the group consisting of: SEQ ID NOs: 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47 and 48 to a subject, wherein said cancer is selected from the group consisting of colon cancer, prostate cancer, and pancreatic cancer." Applicants assert that the claims as amended herein are unobvious over the combination of *eleven* references. Not only does the combination of references fail to teach or

explicitly or implicitly suggest all claim limitations, the combination of references fails to explicitly or implicitly suggest modifying their teachings to arrive at Applicants' invention.

Before addressing the individual teachings of the cited references, Applicants wish to emphasize one of the differences between the teachings of the cited references and what is presently claimed, i.e., that metastases and primary tumors often substantially differ in their gene expression and thus in their reaction to inhibitors. The methods described in the cited prior art documents concern the application of TGF-beta 2 antisense oligonucleotides to treat primary tumors, while the present claims are directed to inhibiting the formation of cancer metastases. Therefore, the combined teachings of these references is not sufficient to render the claimed methods obvious. Based on the combination of references, the person skilled in the art could not have expected that a treatment with TGF-beta2 antisense oligonucleotides might be successful in inhibiting the formation of metastases. To provide evidence in support of these assertions, several abstracts and scientific papers discussing the differences between primary tumors and matched metastases are filed herewith accompanied by a Supplemental Information Disclosure Statement. Of particular interest is Smith et al. 2005, which compares the gene expression of metastatic melanomas to non-metastatic melanomas. Also of particular interest is the abstract of Ujhazy V and Siracky J describing different drug sensitivity in primary tumors and metastases.

The Office Action admits that Schlingensiepen II does not teach administering TGF-β1, 2, and/or 3-specific antisense oligonucleotides to subjects having melanoma. As already mentioned above, the presently claimed TGF-beta2 antisense oligonucleotides represent a *specific* selection, which is not at all rendered obvious from Schlingensiepen II. Even if the antisense oligonucleotides described in Schlingensiepen II were identical to some oligonucleotides of the present invention, Schlingensiepen II does not provide any hint as to which of these oligonucleotides are able to inhibit the formation of metastases. In particular, an oligonucleotide of the present invention has an inhibitory effect on metastases, even if the oligonucleotide does not have an inhibitory effect on the primary tumor, which is definitely not taught or suggested in Schlingensiepen II.

Moreover, the Examiner emphasizes that Schlingensiepen II refers to the effect of the TGF-beta2 antisense oligonucleotides on melanoma and metastases in malignant melanoma, and extrapolates this effect on any metastases of any other type of tumor. However, the treatment and/or prevention of tumors is in fact very difficult and still has a low success rate due to the

high variety of tumors, their ability to form metastases, and their varying sensitivities to drugs. Numerous chemotherapeutics are able to treat the primary tumor, but are not able to inhibit the formation of metastases, and with this in mind, a person skilled in the art would not expect that an oligonucleotide, which is effective in the prevention and/or treatment of a primary tumor, is likewise effective in inhibition of metastases formation.

With regard to Reintgen, this reference does not refer to TGF-beta, to antisense oligonucleotides, or to the inhibition of metastases formation, and its disclosure that malignant melanoma is a form of skin cancer when combined with the remaining ten references fails to render the presently claimed invention obvious. Similarly, Mintz does not mention or provide any hint of TGF-beta2 or antisense technology at all, but describes Tyr-SV40E inducing melanoma. Hence, if a skilled person has the intention to find a solution to the problem underlying the present invention, i.e., finding a successful method for inhibiting the formation of metastases, the skilled person would not have any motivation to combine Schlingensiepen II and Mintz. The skilled person would not have expected that a TGF-beta 2 antisense oligonucleotide, in particular, any of SEQ ID No. 22 to 29, 31 to 35 or 37 to 48, has an effect on the induction of Tyr-SV40 induced melanoma or metastatic melanoma formation.

Paradise, like Mintz, does not mention TGF-beta or antisense technology, and thus provides no hint to an effect of TGF-beta2 on the treatment of metastatic malignant melanoma, and therefore, the skilled person likewise would not have had any motivation to combine Schlingensiepen II and Paradise. The use of a TGF-beta2 antisense oligonucleotide for treating metastatic malignant melanoma is a very different concept from a combination therapy requiring both IL-2 and DTIC, wherein the treatment is based on a synergistic effect of these two compounds.

Swift does not mention TGF-beta or antisense technology, and thus provides no information or guidance about the use of TGF-beta2 antisense oligonucleotides in inhibiting the formation of metastases, and thus, also does not teach any selection of TGF-beta2 antisense oligonucleotides. Thus, a person skilled in the art would not be motivated to combine Schlingensiepen II and Swift. In the event a person skilled in the art would for some reason combine Schlingensiepen II and Swift, he or she would be taught to combine the TGF-beta antisense oligonucleotides of Schlingensiepen II with the benzothiophenes of Swift, resulting in a combination therapy, *not* in the selection of *specific* TGF-beta2 antisense oligonucleotides.

Aylward fails to even mention TGF-beta or antisense technology. Thus, Aylward is not at all directed to the use of TGF-beta2 antisense oligonucleotides for treating cancer, and does not give any hint to the inhibition of metastases formation. Therefore, a person skilled in the art would hardly combine Schlingensiepen II and Aylward to find a solution to the problem underlying the present invention. If the skilled person would combine these documents, he or she would be guided again, at the most, in the direction of a combination therapy including a TGF-beta antisense oligonucleotide and a compound present in plants of the genus Euphorbia. The combination of these documents would not motivate the skilled person to find a *specific* selection of TGF-beta2 antisense oligonucleotides, one or more of which is able to inhibit the formation of metastases.

Brandt emphasizes that antibodies do not necessarily recognize all primary melanomas and melanoma metastases (see col. 1, l. 48-50) as discussed above for antisense nucleotides. Brandt fails to even mention TGF-beta or antisense technology. Brandt is thus completely silent on TGF-beta antisense oligonucleotides and their use in inhibiting the formation of metastases. Therefore, the skilled person would be motivated again to go the direction of a combination therapy, in this case, a combination of a TGF-beta2 antisense oligonucleotide and an anti-GM3 or –GD3 antibody.

As asserted above, McCracken does not provide information about a method of treatment of melanoma or of melanoma metastases, and fails to even mention TGF-beta or antisense technology. Consequently, McCracken does not hint to the use of TGF-beta antisense oligonucleotides in such treatment and thus, a person skilled in the art would not be motivated to combine Schlingensiepen II and McCracken.

As to Fakhrai I, this reference refers to a method of prolonging survival of a subject having a tumor, e.g., melanoma, involving administering a genetically modified cell expressing, for example, TGF-beta antisense nucleic acid. The underlying concept disclosed in Fakhrai I is particularly different from that of the presently claimed invention. In addition, regarding melanoma tumor cells, Fakhrai I discloses MZ2-E (encoding MAGE-1) as a promising target but does not mention TGF-beta in this context (column 8, line 29-31). Fakhrai I does not specify any sequences of TGF-beta antisense oligonucleotides, and does not hint that the method of treatment of tumors is likewise effective in the inhibition of formation metastases. Thus, taken alone, it does not provide any hint to the use of any TGF-beta antisense oligonucleotides,

particularly not those of SEQ ID NO.: 22 to 29, 31 to 35 or 37 to 48 to inhibit the formation of melanoma metastases. Hence, a combination of Schlingensiepen II and Fakhrai I does not guide a person skilled in the art in the direction of the presently claimed invention. In fact, combining these documents, the skilled person would be motivated to prepare genetic constructs expressing the TGF-beta2 antisense oligonucleotides of Schlingensiepen II and to express it in a (tumor) cell according to the method of Fakhrai I. Thus, one would not be motivated to combine Schlingensiepen II and Fakhrai I with the remaining nine references.

Monia is directed to TGF-beta2 antisense oligonucleotides that include phosphorothioate linkages, which are suitable for treating cancer. As mentioned above, Monia does not disclose the specific oligonucleotides of the present invention, which inhibit the formation of metastases, and fails to provide any teaching regarding TGF-beta2 antisense oligonucleotides that are able to inhibit the formation of metastases. If the person skilled in the art combines Schlingensiepen II and Monia, he or she is taught that TGF-beta2 antisense oligonucleotides including a phosphorothioate linkage may be used in the treatment of cancer, not that the presently claimed antisense oligonucleotides lacking this linkage are useful for treating cancer. Combining Monia with the remaining ten references would not lead the skilled person to the selection of the particular, presently claimed TGF-beta2 antisense oligonucleotides for inhibiting the formation of metastases.

Combining Reed with Schlingensiepen II and the remaining nine references would not guide one to modify their teachings to arrive at the presently claimed invention. Reed discloses that metastatic melanomas express TGF-beta2 in addition to TGF-beta1 and TGF-beta3, whereas the primary invasive malignant melanomas do not express universally TGF-beta2 mRNA transcripts; in fact, the expression of TGF-beta2 depends on the tumor stage, wherein TGF-beta2 expression increases with the later stages of the tumor. A skilled person reading Reed would not expect that the inhibition of TGF-beta2 mRNA expression via TGF-beta2 antisense oligonucleotides would reliably inhibit the formation of metastases as not all tumor stages express TGF-beta2. Based on the teachings of Reed, the skilled person would only be motivated to use TGF-beta1 and/or TGF-beta3 antisense oligonucleotides, which are expressed in all stages of the primary tumor. Therefore, combining Schlingensiepen II and Reed with the remaining nine references would not guide or motivate a skilled person to use TGF-beta2 antisense oligonucleotides for inhibiting the formation of metastases.

Even if it would occur to a skilled person to combine the particular eleven documents cited, he or she would not arrive at the presently claimed invention, as combining the teachings of these references would not result in a method for inhibiting the formation of metastases in cancer treatment in a subject comprising the step of administering at least one TGF-beta2 antisense oligonucleotide selected from the group consisting of: SEQ ID NOs: 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47 and 48. The selection of *specific* TGF-beta2 antisense oligonucleotides for inhibiting the formation of metastases is not obvious in view of this combination. Swift describes inhibiting melanoma using a compound without specifically inhibiting the formation of melanoma. Also, Paradise, Aylward, Mintz, Brandt, Fakhrai I, and McCracken are directed to different methods for inhibiting melanoma, but not to methods for inhibiting the formation of metastases.

Even if Monia, Fakhrai I, or Reed teach a correlation between TGF beta2 expression/production and malignant melanoma, none of these documents in combination with Schlingensiepen II guides the skilled person to a method using the presently claimed TGF beta2 antisense oligonucleotides for inhibiting the formation of metastases. Schlingensiepen II, like Monia, Fakhrai I, and Reed, refers to the treatment of primary tumors, but not to the inhibition of formation of metastases, and thus, the combination of these documents does not render the present invention obvious, even if one were to argue that *some* of the oligonucleotides of Schlingensiepen I *might* have inherently had this effect.

Referring again to Reintgen, this reference is solely directed to a method of determining the spread of metastatic melanoma, and combining this document with Schlingensiepen II, a person skilled in the art would at the most select one of the oligonucleotide sequences for the detection of metastatic melanoma. However, the hybridization of an oligonucleotide or an antibody to a target sequence (for detection), does not at all teach if the hybridization results in inhibiting the formation of metastasis. This would be an inaccurate extrapolation to make. This is confirmed, for example, in Fig. 4 A to D of Applicants' recently prepared manuscript entitled "TGF-β2 Gene Silencing with Traverdersen (AP 12009) in Pancreatic Cancer" (filed herewith accompanied by a 1.132 Declaration executed by Dr. Schlingensiepen, and a Supplemental Information Disclosure Statement). These figures show the results of a spheroid migration assay, which show that a TGF-beta2 antibody is not effective in inhibiting the migration of human pancreatic cancer cells, i.e., in inhibiting the formation of metastases, which starts with cell

migration, in comparison to a TGF-beta2 antisense oligonucleotide according to the present invention.

Most of the cited prior art documents were published between 1991 and 2002. If inhibition of the formation of metastases using TGF-beta2 antisense oligonucleotides as presently claimed would have been obvious in view of the combination of eleven references, inhibition of the formation of metastases using TGF-beta2 antisense oligonucleotides would have been described much earlier than the present application, as a strong need for the treatment of metastases exists, not only with regard to melanoma, but also for any other types of metastases.

In summary, the combination of eleven references does not disclose or even implicitly suggest the presently claimed *specific* selection of TGF-beta2 antisense oligonucleotides, which are able to inhibit the formation of metastasis and/or to treat metastasis. Applicants again assert that not all TGF-beta2 antisense oligonucleotides are able to inhibit the formation of metastasis, and that the presently claimed method of inhibiting the formation of metastases in cancer treatment in a subject involving the use of particular TGF-beta2 antisense oligonucleotides is not obvious in view of the combination of eleven references. The claims as amended herein are unobvious over the combination of eleven references, because not only does the combination of references fail to teach or explicitly or implicitly suggest all claim limitations, the combination of references fails to explicitly or implicitly suggest modifying their teachings to arrive at Applicants' invention.

Accordingly, withdrawal of this rejection is respectfully requested.

Claims 23-33 and 39-44 were rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Applic. Pub. No. 2007/0196269 to Schlingensiepen *et al.* ("Schlingensiepen III"), U.S. Patent Applic. Pub. No. 2008/0214483 to Schlingensiepen *et al.* ("Schlingensiepen IV"), each independently in view of Schlingensiepen II, Reintgen, Mintz, Paradise, Swift, Aylward, Brandt, McCracken, Fakhrai I, Monia, and Reed. According to the Office Action:

> Schlingensiepen et al. (US 2007/0196269) and Schlingensiepen et al. (US 2008/0214483) each disclosed antisense oligonucleotides and methods of use thereof within the scope of the instant claims for inihibiting TGF-β2 expression and treating skin carcinogenesis in a subject.

> Prior art references 1-11 are relied on for the reasons given above in the rejection of claims 28-33, 39-42 and 44 under 35 USC 103. As a whole the prior art reasonably suggested inhibiting the expression/production of TGF-β2 using antisense oligonucleotides to treat various forms of cancer, including melanoma, as implied by Schlingensiepen et al. in each of the applications above.
>
> Accordingly, the instant methods would have been prima facie obvious at the time.

Claims 24-26, 31-33 and 39-43 have been canceled. Claim 23 (from which claims 27 - 29 depend) has been amended herein to recite "a method for cancer metastasis treatment comprising the step of administering at least one TGF-beta2 antisense oligonucleotide selected from the group consisting of: SEQ ID NOs: 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47 and 48 to a subject, wherein said cancer is selected from the group consisting of colon cancer, prostate cancer, and pancreatic cancer." Claim 30 has been amended herein to recite a "method for cancer treatment comprising the step of administering at least one TGF-beta2 antisense oligonucleotide selected from the group consisting of SEQ ID NOs: 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47 and 48 to a subject, wherein said at least one TGF-beta2 antisense oligonucleotide inhibits the formation of metastases in said subject and said cancer is selected from the group consisting of: prostate cancer, colon cancer, and pancreatic cancer." Claim 44 has been amended herein to recite a "method for cancer metastasis treatment comprising the step of administering at least one TGF-beta2 antisense oligonucleotide selected from the group consisting of: SEQ ID NOs: 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47 and 48 to a subject, wherein said cancer is selected from the group consisting of colon cancer, prostate cancer, and pancreatic cancer." Applicants assert that the claims as amended herein are unobvious over the combination of *thirteen* references. Not only does the combination of references fail to teach or explicitly or implicitly suggest all claim limitations, the combination of references fails to explicitly or implicitly suggest modifying their teachings to arrive at Applicants' invention.

Applicants wish to again emphasize one of the differences between the teachings of the cited references and what is presently claimed, i.e., that metastases and primary tumors often substantially differ in their gene expression and thus in their reaction to inhibitors. As with the previous rejection, the methods described in the cited prior art documents concern the application

of TGF-beta 2 antisense oligonucleotides to treat primary tumors, while the present claims are directed to inhibiting the formation of cancer metastases. Therefore, the combined teachings of these references is not sufficient to render the claimed methods obvious. Based on the combination of references, the person skilled in the art could not have expected that a treatment with TGF-beta2 antisense oligonucleotides might be successful in inhibiting the formation of metastases (see Smith et al. 2005, and Ujhazy V and Siracky J which describe the differences between primary tumors and matched metastases).

Now turning to the references individually and in combination, Schlingensiepen III refers to a pharmaceutical composition comprising TGF-beta antisense oligonucleotides and at least one substance inhibiting cell proliferation and/or inducing cell death, which is suitable for treating tumors such as melanoma. Schlingensiepen III does not provide any hint to the use of the pharmaceutical composition in inhibiting the formation of metastases, and thus, does not teach specific TGF-beta2 antisense oligonucleotides suitable for inhibiting the formation of metastases. Schlingensiepen III does not provide any information on whether TGF-beta 2 antisense oligonucleotides may indeed be suited for treating melanoma metastases. Moreover, the application solely concerns the treatment of (already formed) primary tumors, whereas the claims of the present application are directed to the inhibition of the formation of metastases. Thus, Schlingensiepen III refers to a different tissue (primary tumor vs. metastases) and to a different approach (inhibiting the formation of cells but not attacking preformed cells). In addition, all experimental data in Schlingensiepen III refer to gliomas only and do not provide any data on other types of tumors, particularly not melanoma metastases (claims 28-30 and 44 are amended herein to recite the particular cancers of colon carcinoma, colorectal carcinoma, pancreas carcinoma, prostate cancer). Given the known (and by the USPTO, commonly cited) unpredictability of cancer treatment in general, Applicants assert that Schlingensiepen III does not provide sufficient information to guide or motivate the person skilled in the art to use the specific, presently claimed TGF-β2 antisense oligonucleotides, i.e., those of SEQ ID NO.: 22 to 29, 31 to 35, and 37 to 48 to inhibit the formation of melanoma metastases. In addition, Schlingensiepen III emphasizes the importance of the synergistic effect of the TGF-beta antagonist and an antineoplastic chemotherapeutic agent (see paragraphs [0223], [0239]). Thus, the methods disclosed in Schlingensiepen III include the administration of at least two substances in combination. The concept of a combination therapy as disclosed in

Schlingensiepen III is completely different from the method of inhibiting formation of metastases of the present invention.

Schlingensiepen IV relates to TGF-beta antisense oligonucleotides, which hybridize with an area of a gene coding for TGF-beta and augments proliferation of cytotoxic lymphocytes or increases cytotoxic responses in a patient. Schlingensiepen IV, like Schlingensiepen III, does not provide any information about specific TGF-beta antisense oligonucleotides for inhibiting the formation of metastases. This is also true for Schlingensiepen II as already mentioned above.

As mentioned above, Reintgen refers to a method for determining the presence of melanocytes in lymph node tissue. Reintgen does not refer to TGF-beta antisense oligonucleotides or the inhibition of metastases formation. Hence, a skilled person would hardly combine Schlingensiepen III or IV with Reintgen with the intention to reach the present invention. Thus, the combination of Schlingensiepen III or IV and Reintgen does not render the present invention obvious.

This is also true for the combination of Schlingensiepen III or IV with Mintz, Paradise, or McCracken. As discussed above, Mintz, Paradise, and McCracken refer to a transgenic animal model for human cutaneous melanoma, to a method for therapeutic treatment of metastatic malignant melanoma comprising administering to a patient a synergistically effective amount of IL-2 and DTIC, and a melanoma detection apparatus, respectively, i.e., completely different aspects than the present invention. Thus, a skilled person would not combine these documents with Schlingensiepen III or IV, and even if he or she did, the combination would not render the present invention obvious. None of these documents provides any hint or suggestion of specific TGF-beta2 antisense oligonucleotides for inhibiting the formation of metastases.

Combining Schlingensiepen III or IV with Swift, Aylward and/or Brandt would not lead a skilled person to the present invention, and consequently, does not render the present invention obvious. Swift refers to a method of inhibiting melanoma, including metastatic melanoma, by using benzothiophenes (2-phenyl-3-aroylbenzothiophenes) in a treatment method, Aylward relates to a compound present in plants of the genus Euphorbia, which is used in a method of treating cancer such as malignant melanoma etc., and Brandt is directed to human monoclonal antibodies and derivatives thereof, which are all specifically binding to gangliosides GM3 and GD3 for treating melanoma and melanoma metastases. Therefore, a combination of Schlingensiepen III and/or IV with Swift, Aylward and/or Brandt teaches the skilled person a

combination therapy. Hence, the combination of these documents, at the most, might render a combination therapy obvious, but not the subject matter of the present application.

Similarly, the combination of Schlingensiepen III and Fakhrai I or II might guide a person skilled in the art to a cell expressing the TGF-beta2 antisense oligonucleotide and to combine it with at least one substance inhibiting cell proliferation and/or inducing cell death. This is a completely different approach for treating a tumor and is not for inhibiting the formation of metastases as is the present invention. With regard to Fakhrai I, the underlying concept is particularly different from that of the presently claimed invention. In addition, regarding melanoma tumor cells, Fakhrai I discloses MZ2-E (encoding MAGE-1) as a promising target but does not mention TGF-beta in this context (column 8, line 29-31). Consequently, the combination of Schlingensiepen III and Fakhrai I and/or II does not render the present invention obvious. This is also true with regard to combining Schlingensiepen IV and Fakhrai I and/or II, which would only result in genetically modified (tumor) cells expressing TGF-beta2 antisense oligonucleotides for the treatment of cancer.

With regard to Monia, while the text mentions the use of oligonucleotides for treating an animal/human "suspected of having or being prone to a disease or condition associated with expression of TGF-beta" (see paragraph [0030]), it does not provide any information that cancer in general or melanoma in particular (not to speak of melanoma *metastasis*) may be such a condition. Monia does not at all describe the specific oligonucleotides of the present invention, which inhibit the formation of metastases. In the unlikely event it would even occur to the skilled person to combine Schlingensiepen III and/or IV with Monia, at most, it might be suggested to the skilled person to use TGF-beta2 antisense oligonucleotides including phosphorothioate either in combination with at least one substance inhibiting cell proliferation and/or inducing cell death (Schlingensiepen III), or without this substance (Schlingensiepen IV). Therefore, this combination of references does not render the present invention obvious.

Finally, Reed discloses, at most, the use of TGF-beta2 antisense oligonucleotides in the treatment of metastases, but does not at all suggest (explicitly or implicitly) inhibiting the formation of metastases. This scientific article describes an expression study of non-metastatic melanoma cells with respect to their expression of TGF-beta 2. The authors report that TGF-beta 2, although expressed in metastatic melanomas, is not necessarily expressed in superficially invasive melanomas and benign melanomas (page 101, column 2, 3rd paragraph). From this, the

authors conclude that the expression of TGF-beta 2 is rather a late event after transformation of the melanoma into an metastatic state and that "TGF-beta 2 reactivity cannot be used with certainty to determine the prior invasive nature" (page 102, column 1, 2nd paragraph). Based on this conclusion in Reed, the person skilled in the art has no reason to believe that antagonizing TGF-beta 2 may indeed inhibit the formation of metastasis (since the expression of TGF-beta 2 only occurs *after* the metastases are already formed). In addition, the authors also emphasize that TGF-beta 1 executes similar functions as TGF-beta 2 and thus is probably able to take over TGF-beta 2 functions (page 102, 2nd column, 1st paragraph). This reference would not guide the person skilled in the art to develop a method using oligonucleotides against TGF-beta 2 in general, and certainly would not guide one towards using the particular sequences of SEQ ID NO.: 22 to 29, 31 to 35 and 37 to 48 that are presently claimed, for a therapy inhibiting the formation of metastases. Thus, combining Reed and Schlingensiepen III and/or IV might result in the use of those specific TGF-beta2 antisense oligonucleotides disclosed in Schlingensiepen III and/or IV, but not in their use for inhibiting the formation of metastases. Combining these references with the remaining references also fails to render the present invention obvious.

On page 26 of the Office Action, the Examiner asserts that "the method suggested by the prior art meets all the limitations in the claims, including the functional limitation of inhibiting metastases." The claims have been amended herein to recite "inhibiting the formation of metastases" or "inhibits the formation of metastases," and Applicants assert that the method suggested by the prior art does not meet all the limitations in the claims, e.g., inhibiting the formation of metastases.

In summary, the combination of thirteen references does not disclose or even implicitly suggest the presently claimed *specific* selection of TGF-beta2 antisense oligonucleotides, which are able to inhibit the formation of metastasis. Applicants again assert that even if it would occur to one of skill in the art to combine all thirteen documents, this combination would not lead to the present invention as the combination fails to implicitly or explicitly suggest a method for inhibiting metastases formation using the specific, presently claimed TGF-beta2 antisense oligonucleotides. Not all TGF-beta2 antisense oligonucleotides are able to inhibit the formation of metastasis, and thus the presently claimed method of inhibiting the formation of metastases in cancer treatment in a subject involving the use of particular TGF-beta2 antisense oligonucleotides is not obvious in view of the combination of thirteen references. The claims as

amended herein are unobvious over the combination of thirteen references, because not only does the combination of references fail to teach or explicitly or implicitly suggest all claim limitations, the combination of references fails to explicitly or implicitly suggest modifying their teachings to arrive at Applicants' invention.

Accordingly, withdrawal of this rejection is respectfully requested.

Claims 28-32, 39, 40, 42 and 44 were rejected under 35 U.S.C. 103(a) as being unpatentable over Monia, and further in view of Fakhrai I and U.S. Patent No. 7,101,543 to Fakhrai *et al.* ("Fakhrai II"). According to the Office Action:

> One of skill would immediately have recognized that the antisense oligonucleotide that inhibits TGF-β2 is the active agent responsible for the cancer treatment effect, and that the means by which the antisense is introduced or delivered is simply an expedient and a matter or design choice to maximize and sustain antisense-mediated inhibition of the target gene. Accordingly, one of skill would reasonably have expected that any effective means known in the art for delivering an antisense oligonucleotide into a subject in an amount effect to reduce TGF-β2 production as required for cancer treatment would produce substantially the same effect as that disclosed by Fakhrai et al., given that Monia et al. disclosed and recommended numerous such routes by which to deliver an oligonucleotide.
>
> All effects inherent to the use of antisense oligonucleotides that inhibit TGF-β2, including those recited in the instant claims, such as inhibition of metastasis formation, would necessarily be obtained by the administration of such oligonucleotides, since a compound and its properties are inseparable, and since, as evidenced by instant claim 25, the inhibition of TGF-β2 inhibits formation of metastases (MPEP 2112).

Applicants respectfully disagree with these assertions, and point the Examiner to MPEP Section 2112 which is entitled "EXAMINER MUST PROVIDE RATIONALE OR EVIDENCE TENDING TO SHOW INHERENCY." The following text is copied directly from MPEP Section 2112:

> The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or

characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted).

Also, "[a]n invitation to investigate is not an inherent disclosure" where a prior art reference "discloses no more than a broad genus of potential applications of its discoveries." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004) (explaining that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category" but must be examined to see if a disclosure of the claimed species has been made or whether the prior art reference merely invites further experimentation to find the species.

"In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original) (Applicant's invention was directed to a biaxially oriented, flexible dilation catheter balloon (a tube which expands upon inflation) used, for example, in clearing the blood vessels of heart patients).

Applicants assert that the characteristic of metastases formation inhibition by the specific TGF-β2 antisense oligonucleotides currently claimed does not necessarily flow from the teachings of the cited references or the combination thereof, and that the claims as amended herein are unobvious over the combination of Monia, Fakhrai I, and Fakhrai II. Not only does the combination of references fail to teach or explicitly or implicitly suggest all claim limitations, the combination of references fails to explicitly or implicitly suggest modifying their teachings to arrive at Applicants' invention. Claims 31, 32, 39, 40, and 42 have been canceled. Claim 23 (from which claims 27 - 29 depend) has been amended herein to recite "method for cancer metastasis treatment comprising the step of administering at least one TGF-beta2 antisense

oligonucleotide selected from the group consisting of: SEQ ID NOs: 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47 and 48 to a subject, wherein said cancer is selected from the group consisting of colon cancer, prostate cancer, and pancreatic cancer." Claim 28 has been amended herein to recite "the method of claim 23, wherein said cancer is selected from the group consisting of colon carcinoma, colorectal carcinoma, pancreas carcinoma, and prostate cancer." Claim 30 has been amended herein to recite a "method for cancer treatment comprising the step of administering at least one TGF-beta2 antisense oligonucleotide selected from the group consisting of SEQ ID NOs: 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 33, 34, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47 and 48 to a subject, wherein said at least one TGF-beta2 antisense oligonucleotide inhibits the formation of metastases in said subject and said cancer is selected from the group consisting of: prostate cancer, colon cancer, and pancreatic cancer."

Applicants wish to again emphasize one of the differences between the teachings of the cited references and what is presently claimed, i.e., that metastases and primary tumors often substantially differ in their gene expression and thus in their reaction to inhibitors. As with the previous rejections, the methods described in the cited prior art documents concern the application of TGF-beta 2 antisense oligonucleotides to treat primary tumors, while the present claims are directed to inhibiting the formation of cancer metastases. Therefore, the combined teachings of these references is not sufficient to render the claimed methods obvious. Based on the combination of references, the person skilled in the art could not have expected that a treatment with TGF-beta2 antisense oligonucleotides might be successful in inhibiting the formation of metastases (see Smith et al. 2005, and Ujhazy V and Siracky J which describe the differences between primary tumors and matched metastases).

With regard to Fakhrai I, the underlying concept (administering a genetically modified cell containing a genetic construct expressing a TGF-beta2 inhibitor such as an antisense molecule) is particularly different from that of the presently claimed invention. In addition, regarding melanoma tumor cells, Fakhrai I discloses MZ2-E (encoding MAGE-1) as a promising target but does not mention TGF-beta in this context (column 8, line 29-31). Fakhrai I discloses that administering modified cells is advantageous, i.e., is particularly useful due to high levels of sustained expression of the antisense nucleic acid sequences (see col. 12, l. 48-50). Fakhrai I

does not teach or suggest a method for inhibiting the formation of metastases using specific TGF-beta2 antisense oligonucleotides.

Monia is directed to TGF-beta2 antisense oligonucleotides comprising, for example, a phosphorothioate linkage, for use in a method of treating cancer. Monia does not hint to the use of specific TGF-beta2 antisense oligonucleotides for use in inhibiting the formation of metastases as already mentioned.

As neither Monia nor Fakhrai I provide any information in that direction, a combination of these documents does not render the present invention obvious. Further, as it is well known for a skilled person that an oligonucleotide is very vulnerable with regard to degradation via exo- and endonucleases, a person skilled in the art would have avoided using an antisense oligonucleotide as such in "pure" form without any liposomes, carriers etc. Hence, the use of the TGF-beta2 antisense oligonucleotide in the present invention is not at all an obvious alternative with regard to Monia and Fakhrai I.

As for Fakhrai II, this reference discloses an exogenic tumor cell which is used as a vaccine, and that only the exogenic cell's TGF-beta levels are reduced, not those of the patient's endogenous cancer cells. In addition, the description neither mentions the treatment of melanomas in general nor the inhibition of the formation of melanoma metastases in particular. Adding Fakhrai II to the combination fails to cure the deficiencies of Fakhrai I and Monia. In Fakhrai II, which refers to a composition for prolonging survival of a subject like Fakhrai I, the tumor has been specified as lung cancer, and thus, the preferably modified cells expressing a TGF-beta antisense inhibitor are lung cells like NSCLC or SCLC. Fakhrai II also fails to provide any hint to or a suggestion of a method of inhibiting formation of metastases using specific TGF-beta2 antisense oligonucleotides, and therefore, the combination of Monia, Fakhrai I, and Fakhrai II does not lead to the present invention.

In summary, the combination of Monia, Fakhrai I and Fakhrai II does not disclose or even implicitly suggest the presently claimed *specific* selection of TGF-beta2 antisense oligonucleotides, which are able to inhibit the formation of metastasis. Applicants again assert that even if it would occur to one of skill in the art to combine these three documents, this combination would not lead to the present invention as the combination fails to implicitly or explicitly suggest a method for inhibiting metastases formation using the specific, presently claimed TGF-beta2 antisense oligonucleotides. Not all TGF-beta2 antisense oligonucleotides are

able to inhibit the formation of metastasis, and the presently claimed method of inhibiting the formation of metastases in cancer treatment in a subject involving the use of particular TGF-beta2 antisense oligonucleotides is not obvious in view of the combination of references. The claims as amended herein are unobvious over the combination of references, because not only does the combination of references fail to teach or explicitly or implicitly suggest all claim limitations, the combination of references fails to explicitly or implicitly suggest modifying their teachings to arrive at Applicants' invention.

Accordingly, withdrawal of this rejection is respectfully requested.

Conclusion

The currently pending claims are supported throughout the specification and are patentable over the prior art. No new matter has been added. This application is now in full condition for allowance, and such action is respectfully requested.

A Request for a Retroactive Extension of Time is filed herewith. A credit card payment is made herewith for the required fee. However, the Commissioner for Patents and Trademarks is hereby authorized to charge any underpayment of fees or credit any overpayment of fees to Deposit Account No. 14-1437.

Respectfully submitted,

/Amy Dobbelaere/

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